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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,568	10/01/1998	RANDOLPH J. NOELLE	012712-572	6823

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/164,568	NOELLE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/24/06 and 4/12/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *82-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 3/24/06, has been entered.
Claim 82 has been amended.

Claims 82-94 are pending and being acted upon presently.

Claims 1-81 have been canceled previously.

2. This Office Action serves as a response to applicant's Status Inquiry, filed 4/12/06.

However, it is unclear why applicant is requesting a Status Inquiry within one (1) month of filing an amendment.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 3/24/06.
The rejections of record can be found in previous Office Action, mailed 1/5/06.

4. Applicant's amended claims now recite "human gp39", wherein "human gp39" is "human gp39" also called "CD40 ligand or CD40L" as disclosed on page 2, paragraph 3 and page 7 of the instant specification.

The filing date of the instant claims drawn to "human gp39" is deemed to be the filing date of parent application USSN 08, 232,929, i.e. 4/24/1994.

Priority application USSN 08/116,255 does not support the instant claims drawn to "human gp39" of the instant application.

If applicant desires priority prior to 4/24/1994; applicant is invited to point out and provide documentary support for the priority of the instant claims.
Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Furthermore, applicant is also reminded of the holding in Noelle v. Lederman, 355 F.3d 1343, 1349-1350 (Fed. Cir. 2004).

5. Applicant's amended claims, filed 3/24/06, to recite the mouse / human gp39 as set forth on pages 2 and 7 of the instant specification have obviated the previous rejections under 35 USC § 112, first paragraph, written description and enablement.

6. Applicant's amended claims, filed 3/24/06, to recite the mouse / human gp39 as set forth on pages 2 and 7 of the instant specification have obviated the previous rejections under 35 USC § 112, second paragraph.

7. With respect to the previous rejection under 35 U.S.C. § 103 and as noted by applicant's amendment, filed 3/24/06, the previous references Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) are no longer at issue in view of the newly amended claims drawn to "mouse / human gp39".

Therefore, Armitage et al. (U.S. Patent No. 6,264,951) OR Aruffo et al. (U.S. Patent No. 6,376,459) has been withdrawn from the previous rejection under 35 U.S.C. § 103.

8. Claims 82-94 are rejected under 35 U.S.C. § 103 as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091) in view of Berschorner et al. (U.S. Patent No. 5,597,563), Cobbold et al. (U.S. Patent No. 5,690,933) and Enyon et al. (J. Exp. Med. 175: 131-138, 1992) for the reasons of record.

The following is a reiteration of the previous Office Action for applicant's convenience.

Applicant's arguments of record have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argued that the prior art did not provide sufficient motivation and expectation of success at the time the invention was made for the claimed methods.

Applicant argued that Enyon's T cells are not activated and therefore do not express gp39 and therefore is irrelevant to any tolerization process involving T cells expressing gp39 since there would be no need to administer an activated T cell inhibitors if T cells never became activated in the first place due to the lack of co-stimulatory signal. Applicant further asserted that the tolerance taught by Enyon requires the use of an adjuvant and that temporary tolerance as described would be fairly worthless from a therapeutic perspective. Applicant asserted that given the teachings of Enyon, there would be no motivation to administer an anti-gp39 antibody.

Again it was noted that Enyon et al. teach that B cell presentation of antigen in the absence of appropriate help leads to antigen-specific T cell anergy in vivo (see entire document). Here, Enyon et al. also acknowledge the art-known role of B cells as APCs, including B cell involvement in tolerance induction in skin graft survival (see page 131, column 2, paragraph 1). Enyon et al. also note that antigen-specific B cells are involved in tolerance induction (page 132, column 1, lines 11-17).

In contrast to applicant's assertions concerning the limitations of Enyon, the teachings of Enyon et al. are not limited to specific therapeutic regimens. Rather, Enyon et al. does provide sufficient motivation and expectation of success that B cells, including both antigen-specific B cells and small resting B cells can serve as antigen presenting cells in tolerizing regimens. Enyon et al. also teach a role for small B cells as antigen-specific tolerizing antigen-presenting cells in acquired self-tolerance soluble self-proteins (see Abstract and last paragraph of Discussion).

Given that Berschorner's tolerization process is based on depletion of dendritic cells (APCs) in the thymic medulla using an immunosuppressant followed by recruitment or infusion of new APCs to thymus while treating with various stimulating growth hormones, applicant argued that anti-gp39 antibody would have deleterious effects on Berschorner's tolerization process. Applicant assertions that Berschorner teaches away from the claimed methods since Bershcorner's methods of not administering an immunosuppressant along with APCs were in direct contravention to the presently claimed methods and further asserts that both methods are mutually exclusive of one another.

Again, Berschorner teach the use of antigen containing antigen-presenting cells for inducing tolerance to autoantigens or self antigens in the treatment of autoimmune diseases by administering the said antigen containing antigen presenting cells and an immunosuppressive (see entire document, including Detailed Description and Claims). Beschorner also teach that the antigen presenting cells include dendritic cells, Langerhans cells and mononuclear phagocytes (see column 6, paragraph 3), encompassed by the claimed methods. While Berschorner is direct to a goal of inducing antigen-specific tolerance while minimizing risk to the animal that is normally associated with protracted immunosuppressive therapy, it is noted that Berschorner acknowledges that immunosuppressive therapy was the standard therapy at the time the invention was made (see Background of the Invention and Summary of the Invention).

Applicant argued that Cobbold's teachings are irrelevant to anti-gp39 antibodies, since these teachings cannot be extrapolated to antibodies against any T cell antigen, particularly to antibodies that inhibit gp39, which were believed to only inhibit T cell's activation of a B cell.

Again, Cobbold et al. teach that specific non-responsiveness can be induced to a self antigen or antigens in order to treat autoimmune diseases by administering immunosuppressive antibodies and antigen (see entire document, including column 3, paragraph 4). Cobbold et al. also note that persistent antigen is require to maintain tolerance, which applies to self (auto) antigens in the treatment of autoimmune diseases (column 3, paragraph 5). Cobbold et al. teach antigen presenting cells can be isolated from the bone marrow, blood, thymus, epidermis, liver, fetal liver or spleen (see column 6, paragraph 3). In contrast to applicant's assertions, Cobbold et al. provides direction to inducing tolerance via the inhibition of T cells. Furthermore, the CD40L was not known at the priority date of Cobbold et al.

Applicant argued that the each and every one of the anti-gp39 antibodies have any effect on T cell responsiveness and asserted that these references only teach anti-gp39 antibodies may reduce B cell activation.

In contrast to applicant's assertions, Lederman et al. provides for methods for inhibiting the rejection of transplant organs (see column 11, paragraph 6 and Claims) in a subject with 5c8-specific antibodies (i.e. CD40 ligand- / gp39-specific antibodies) in addition to methods of the autoimmune response (see column 11, paragraph 7).

Applicant submitted that the combination of references is incongruent and fails to teach the methods of the present claims.

Contrary to applicant's assertions that teachings of Enyon, Beschorner and Cobbold do not support a general conclusion that APCs can be administered to induce tolerance with gp39-specific antagonists with sufficient motivation and expectation of success at the time the invention was made, the following of record was noted for applicant's convenience.

It was also known that CD40 the ligand for gp39 (CD40 ligand) is present on other APCs such as dendritic cells, which are intimately involved in the induction of T cell immunity or tolerance. In addition, gp39 was known to be expressed mainly by activated T helper cells and a number of $CD8^+$ cells as well. Therefore, it was known that one could use gp39 antagonists to block T cell-mediated activation and that the appropriate in vivo APCs such as B cells and dendritic cells, which express CD40, would be subject to such manipulation. It was well known in the art at time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity.

With respect to applicant's request for the support that "it was well known in the art at the time the invention was made that the provision of signal 1 (antigen) in the absence of signal 2 (help) would lead to some form of tolerance rather than immunity", applicant is invited to look no further than the Background of the Instant specification, including page 2, paragraph 1.

As indicated above, applicant acknowledges that APCs can provide antigen to induce tolerance or specific non-responsiveness in various contexts and systems at the time the invention was made.

Contrary to applicant's assertions, the prior art provide sufficient motivation and expectation of success that providing an immunosuppressive regimen, including antagonistic antibodies, in combination with APCs can induce tolerance or antigen-specific nonresponsiveness.

Here, the teachings of Lederman et al. clearly provide for anti-CD40L (anti-5c8, anti-gp39, anti-CD40 ligand) antibodies to inhibit the immune response in order to treat various disease conditions, such as autoimmunity. These teachings are consistent with the teachings of Enyon, Beschorner and Waldmann to provide APCs to induce tolerance to antigens of interest under the cover of immunosuppression at the time the invention was made.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill

in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the primary references pertaining to the treatment of disease conditions such as autoimmunity and the teachings of the secondary references indicating the success of employing APCs to induce tolerance or specific antigen to solve a similar problem of treating autoimmunity would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art of inducing long term non-responsiveness to autoantigens in such individuals having autoimmunity. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to applicant's assertions of teaching away by the prior art because the references are directed to alternative tolerance induction regimens, there is insufficient discouragement nor skepticism in the prior art for employing various antigen presenting cells, including those known in the prior art and encompassed by the claimed methods, in the induction of tolerance to antigens of interest, including autoantigens. Furthermore, various immunosuppressive regimens associated with tolerance induction regimens were known and practiced at the time the invention was made to achieve this highly desirable goal.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of an autoantigen containing antigen presenting cells and a gp39-specific antibody to induce antigen-specific non-responsiveness to autoantigens as a treatment for autoimmunity by providing persistent autoantigens under the cover of immunosuppressives, since both contribute to long term antigen non-responsiveness in the treatment of autoimmunity.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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